REMARKS

Status of the Claims

Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, 115-157 are in the application.

Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, 115-157 were rejected.

By way of this amendment, claims 67-72, 75, 76, 84-86, 94-96 and 126-140 have been canceled, claim 148 has been amended, and new claims 158-165 have been added.

Upon entry of this amendment, claims 58, 59, 63, 64, 115-125 and 141-165 will be pending.

Summary of the Amendment

The claims have been amended to more specifically define aspects and embodiments of the invention.

Claims 67-72, 75, 76, 84-86, 94-96 and 126-140 have been canceled without prejudice.

Claim 148 has been amended to recite the generation of an antibody in response to an antigen instead of referring more generally to the generation of an immune response.

New claims 158-165 have been added to define specific embodiments of the invention. Support for the amendment is found throughout the specification and claims as originally filed. No new matter has been added.

Rejection under 35 U.S.C §112

Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, 115-157 stand rejected under 35 U.S.C §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is asserted that the specification, while "***being enabling for the production of antibodies*** for non-therapeutic purposes, does not reasonably provide enablement for the therapeutic immunization of an animal." (Final Office Action, page 6, emphasis added). In the Advisory Action, after Applicants attempted to amend

the Application to remove any mention of protective or therapeutic immunity (Amendment was not entered), the Office stated, "The limitation of protective or therapeutic immunity, while not specifically claimed, must still be broadly construed to be embraced by the base claims 58, 115 and 148." (Advisory Action, page 3) The Office alleges that undue experimentation would be required to practice the invention. Applicants respectfully disagree

As an initial matter, Claims 67-72, 75, 76, 84-86, 94-96 and 126-140, which were directed at methods of immunizing an individual have been canceled and the rejection is moot as applied to those claims. Applicants respectfully assert the remaining claims are in condition for allowance.

As described in the M.P.E.P.

> The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The ***invention*** that one skilled in the art must be enabled to make and use is that ***defined by the claim(s)*** of the particular application or patent.

(M.P.E.P § 2164, emphasis added). Accordingly, the claims should be examined to determine whether or not the invention as defined by the claims is enabled by the specification. There is no requirement that requires Applicants to enable additional limitations that may or may not be present in various embodiments of the invention. The rejection of the instant claims under the first paragraph of §112 is based upon limitations not found in the claims. "***Limitations may not...be imported into the claims from the specification.***" (M.P.E.P. § 2163). The rejection is based upon examination of limitations not present in the claims, which is ***strictly*** prohibited by the M.P.E.P and the Courts.

As stated above, it has been acknowledged in the Office Action that the specification enables the present invention as defined by the claims, i.e. the specification teaches how to make and use compositions and practice methods for the production of antibodies. The claims are in compliance with 35 U.S.C §112, first paragraph. The rejection is improper as being directed to limitations not included in the claims.

It is well accepted that the production of antibodies has other uses besides providing active immunity (i.e. protective or therapeutic) in the individual which the DNA is injected into. While, active immunity is one reason for generating antibodies, it is not the only reason one of skill in the art would generate antibodies in an individual.

Passive immunity is different from active immunity, in that the antibodies generated against an antigen can be removed from the host and used for other purposes (i.e. administered to another individual or host). Examples of this are prevalent in the immunological industry. For example, tetanus antitoxin is an antiserum that has been produced by actively immunizing an animal with tetanus toxoid. This antiserum containing antibodies generated against an antigen may be used when an animal is exposed to spores of the tetanus bacillus (*e.g.* in a dirty puncture wound) and has not been actively immunized with tetanus toxoid. A physician, believing that disease symptoms may occur before the patient is able to mount an active immune response, will inject the tetanus antiserum in order to provide immediate protection. Although the protection may be finite the initial protection can be crucial to preventing an individual from contracting the disease.

Passive immunity can also be used to aid in the protection an individual from a wide range of diseases. Immune globulin (IG) can be prepared from the gamma globulin fraction of pooled plasma from the blood of several thousand blood donors on the assumption that the large pool will contain good levels of antibodies against many common diseases such as hepatitis A, measles, rubella. Antibodies generated in one individual and administered to another individual has also been used extensively in patients that are immune compromised. For example, patients with either X-linked agammaglobulinemia, common variable immunodeficiency, or immunodeficiency with hyper-IgM, have been treated with intravenous immunoglobulins. Two such studies found that intravenous immunoglobulin replacement therapy is "***effective in preventing*** severe acute bacterial infections and pulmonary insufficiency" (J. Pediatrics (1999) **134**:589-96, see attached abstract, emphasis added) and "the severity and frequency of infections, even in patients with chronic lung disease, ***decreased significantly***." (Turk J.

Pediatrics (1992) **34**:203-9, see attached abstract, emphasis added). Another study showed that antibodies administered from another individual in a passive fashion have long enough half-lives to be protective (see, Abstract, Monogr Allergy (1998) **23**:225-235).

Additionally, some preparations of immune globulin are harvested from specific individuals who have either recently recovered from a disease or who have been deliberately and intensively immunized against it. These are used to provide protection against diseases such as rabies, tetanus, varicella (chicken pox), and the like.

Antibodies generated by passive immunity are also used to prevent Rh-negative mothers from becoming sensitized to the Rh antigen of their newborn child. These uses of passive immunity are well known to one of ordinary skill in the art. Examples of products produced for commercial use include, for example, several products produced by the Bayer company, which makes and manufactures several human immunoglobulin products to protect against diseases including, Hepatitis A, Rabies, and Measles (see, attached print outs from Bayer). Therefore, the present invention describes, for example, a new way to produce antibodies that can be used for products such as these.

It is abundantly clear that one of ordinary skill in the art would understand that the pending claims are enabled to produce antibodies in an individual, which the Examiner agrees (see above), and that these antibodies can be useful for uses such as passive immunity and the examples described above.

It is well accepted that the specification must enable the ***claimed invention***. Although the present specification discusses protective and therapeutic immunity these elements are not present in the pending claims. The pending claims are directed to a pharmaceutical composition (claim 58), a method of introducing DNA molecules into cells of an individual (claim 115), and a method of inducing antibodies against an antigen (claim 148). The remaining claims depend on one of these claims and define more specific embodiments of the invention. The specification enables one of skill in the art to be able to make and use the claimed invention as defined by the pending claims. ***None*** of the claims recites "A method of inducing protective or therapeutic

immunity." These limitations do not appear in the claims and, as discussed above, "***Limitations may not...be imported into the claims from the specification.***" (M.P.E.P. § 2163).

The Court of Appeals for the Federal Circuit (CAFC) has been very consistent on the standard of enabling a claim for what is written in the claim and not what is might be used for. The court has stated:

> Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect..."***The enablement requirement is met if the description enables any mode of making and using the claimed invention.***".

(*CFMT Inc. v. Yieldup International Corp.*, 68 USPQ2d 1940 (CAFC 2003)), citations omitted, emphasis added). The present enablement rejection is based on a limitation that is "absent" from the pending claims, which according to the courts is improper. In *Bio-Technology General Corp. v. Genentech Inc.*, 60 USPQ2d 1430 (CAFC 2001) the court found that a "claim ...read in light of the specification, [that] neither requires nor excludes" a certain element, the fact that the claimed process may produce an additional element (i.e. protective or therapeutic immunity) "***does not invalidate the claims for lack of enablement.***" (*Id.*, emphasis added). The present specification and the claims "neither requires nor excludes" protective or therapeutic immunity and, therefore, the claims should be not be found to lack enablement.

In the present application the current claims are directed to methods of inducing antibodies. The fact that the claimed method might be used to produce protective or therapeutic immunity is tangential to the enablement requirement of the pending claims. The Office has done that which is prohibited by the courts, requiring that a claim be enabled for a process that is ***not*** claimed, not required, or excluded by the claims or the specification.

The Office has failed to provide any reasoning or evidence as to why the pending claims when read correctly (*i.e.* without importing the "absent" limitations) are not enabled. In fact, the Office acknowledges that one skilled in the art would reasonably expect the invention as claimed can be used to induce antibodies against an antigen in an individual. An individual that is

injected with a DNA molecule and a polynucleotide function enhancer of the present invention would be expected to have an immune response that would result in antibodies being produced against the antigen. Protective immunity or therapeutic immunity is not required. However, making and using the present invention to induce antibodies may have a protective or therapeutic response. Either way, the claims to methods of inducing an antibody response would cover the method. The only requirement for the pending claims to be enabled is that one of skill in the art would know how to make and use the invention to induce antibody production in an individual. This is clearly enabled by both the specification and by the knowledge of one of ordinary skill in the art. Those having ordinary skill in the art would accept the objective truth of Applicants' assertions in view of totality of the evidence.

Accordingly, since the pending claims do not recite elements requiring protective or therapeutic immunity, and the claims ***are enabled*** to one of ordinary skill in the art to make and use present invention to induce antibodies, the claims satisfy the requirements under 35 U.S.C. § 112, first paragraph. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

Rejection under 35 U.S.C §103

Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Felgner *et al.* (U.S. Patent No. 6,214,804, hereinafter the "Felgner reference") in view of Price *et al.* (PNAS (1987) 84:156-160, hereinafter the "Price Reference")and Booth *et al.* (WO 91/12329, hereinafter the "Booth reference). The Examiner alleges that the '804 patent discusses a method of introducing a pathogenic antigen into an individual for the production of an immune response including the production of antibodies, but does not discuss a polynucleotide function enhancer. The Examiner alleges that WO 91/12329 discusses introducing a DNA molecule and polynucleotide function enhancer to cells of a host and that Price *et al.* discusses the plasmid of WO 91/12329 encoded a viral antigen from an intracellular pathogen. The Examiner concludes that it would have allegedly been

obvious to combine the teachings of the above mentioned references to get the claimed inventions. Applicants respectfully disagree

As an initial matter, Claims 67-72, 75, 76, 84-86, 94-96 and 126-140 have been canceled and the rejection is moot as applied to those claims. Applicants respectfully assert the remaining claims are in condition for allowance.

The remaining claims are not obvious because the references cited by the Office fail to provide motivation to one of skill in the art to combine the references because the references teach away from one another, thereby preventing them from being combined. The Felgner reference teaches away from using the technology described in the Booth reference. The Felgner reference not only does not provide motivation for one of skill in the art to combine the references, it expressly instructs the skilled artisan not to use the technology described in the Booth reference. Even if one reference teaching way from another was not enough to convince the Office to withdraw its rejection under 35 U.S.C. § 103, which it is, the Booth reference also teaches away from using the technology described in the Felgner reference. The Booth reference not only does ***not*** provide motivation for one of skill in the art to combine the references, it expressly instructs the skilled artisan not to use the technology described in the Felgner reference. It is well established law that references that teach away from each other cannot be combined to establish a *prima facie* case of obviousness. "[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant" (*Sibia Neurosciences Inc. v. Cadus Pharmaceutical Corp.* (CA FC) 55 USPQ2d 1927, citations omitted). Therefore, since ***both*** the Booth and Felgner references teach that the "line of development" from each other is "unlikely to be productive" the references would not be combined by one of ordinary skill in the art. Therefore, the present invention is not obvious. Furthermore, the Price reference does not provide the motivation to combine the references because the Price reference only discusses using retroviral vectors.

Contrary to the accepted law, the present rejection has been maintained even in response to Applicants' arguments and evidence to the contrary that the present invention is not obvious. In Applicants' previous response, Applicants respectfully pointed out that the Booth reference teaches away from using a DNA molecule with a polynucleotide enhancer because the Booth reference states, "The treatment of genetically-related diseases with techniques as DNA transfection has thus far, unfortunately, not met with great success." (page 7, lines 24-26). The specification goes on to describe the extreme limitations of using DNA techniques and does not discuss introducing DNA with a polynucleotide function enhancer. The Office alleges that the statements by the Booth reference cannot "be construed as teaching away" (Final Office Action, page 24), but rather the Office interprets the Booth reference in a way that "simply provides a method for improving delivery of a desired gene to a target cell in an animal, and is silent as to the use of the polynucleotide function enhancer in combination with DNA." (Final Office Action, page 23). The Office also alleges that because the Booth reference discusses deficiencies in retroviral systems prior to the invention described that Booth was just summarizing the prior art and not teaching away, but instead was merely silent to using the polynucleotide function enhancer with DNA molecules. However, the Booth reference is not silent as to the ineffectiveness of DNA as the above statement of "not met with great success" illustrates. The Booth reference describes ***only*** experiments using a retroviral vector. Therefore, there are no suggestions within the Booth reference either implicitly or explicitly that a polynucleotide function enhancer can be combined with DNA. A retroviral vector and a DNA molecule have very different properties, including the requirement that a retroviral vector requires a dividing cell for gene expression, while a DNA molecule does not. Taking the Booth reference as a whole would lead one of ordinary skill in the art to believe that combining the polynucleotide function enhancer with DNA would be a waste of time and money because the Booth reference disparages techniques using DNA plasmids or vectors.

The Office also alleges that since the Felgner reference "contemplated use of RNA in a method of delivery of a gene to a cell of an animal," that one of skill in the art would have been

motivated to combine the references. However, even though Felgner discusses using a naked RNA molecule, specifically an mRNA molecule (column 4, lines 57-58), the Felgner reference does not describe administering a retrovirus. Rather Felgner ***teaches away*** from using retroviruses, like those discussed in the Booth reference, by stating:

> The clinical application of gene therapy, as well as the ***utilization of recombinant retrovirus vectors***, has been delayed because of safety considerations. Integration of exogenous DNA into the genome of a cell [by retroviruses] can cause DNA damage and possible genetic changes in the recipient cell that could predispose to malignancy. A method which ***avoids these potential problems*** would be of significant benefit in making gene therapy safe and effective.

(Felgner, Col. 1, lines 38-45, emphasis added). Therefore, two of the three references cited by the Office teach away from using the other's "line of development" to drive gene expression. Instead of providing motivation to combine, the Felgner and Booth references actually provide motivation ***not*** to combine based on the negative comments the references use against the other's technology.

The Office alleges that the motivation to combine the references is "provided by Booth *et al.*, where Booth *et al.* teach the increased expression of the desired gene by use of the polynucleotide function enhancer." (Office Action, page 25). Applicants respectfully assert that this is incorrect. The Booth reference does not provide motivation to combine or modify the reference to produce the claimed invention because of the different compositions that are being used to drive gene expression. The fundamental difference between the Booth reference and the present invention (*i.e.* retrovirus *v.* DNA molecule) cannot be ignored. One of skill in the art would not have been motivated to combine the references because there is nothing in the Booth reference that suggests using the polynucleotide functional enhancer with a naked nucleotide molecules (*i.e.* RNA or DNA). And along with the Felgner's warning against using a retrovirus, the motivation to combine the references simply does ***not*** exist.

The Price reference also fails to provide motivation to one of skill in the art to combine the references. The Price reference discusses lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer. The Price reference does not discuss using a DNA molecule to induce antibodies or to express a gene. The Price reference does not discuss using a DNA molecule with a polynucleotide function enhancer. The Price reference also does not suggest either explicitly or implicitly to a person of ordinary skill in the art to combine and/or modify the references cited by the Office to yield Applicants' invention. Therefore, the Price reference fails to overcome the deficiencies of the Booth and Felgner references.

Applicants respectfully assert that the Office is not reading the references as a whole, but is rather choosing particular elements from each reference to yield the present invention. However, picking and choosing elements from a reference without considering the reference in its entirety is improper. "A prior art reference must be considered in its entirety, i.e., as a whole, ***including portions that would lead away from the claimed invention***." (M.P.E.P § 2141.02, emphasis added) When one of skill in the art reads the references in their ***entirety***, the skilled artisan would ***not*** be motivated to combine the references.

Even if the Office had shown that there were a motivation to combine the references, which it has not, the Office has not demonstrated that one of ordinary skill in the art would have had an expectation of success. As admitted by the Office, the Booth reference is "silent about the use of a polynucleotide function enhancer with naked DNA." (Office Action, page 24). Since the Booth reference only describes examples using retroviral vectors, one of skill in the art could have expected that it would only work with a retrovirus and not with a naked DNA molecule, especially in view of the fact that naked DNA and a retroviral vector have very different properties (for example, a retrovirus needing a mitotically-active cell, while naked DNA does not). Therefore, one of skill in the art would not have had an expectation of success when combining the references cited by the Office.

Accordingly, since the Office has failed to demonstrate that one of skill in the art would have been motivated to combine the references or that one of skill in the art would have had an

expectation of success and combined with the facts that both the Felgner and Booth references teach away from using one another, the present invention is not *prima facie* obvious.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Non-statutory Double Patenting

Various claims have been rejected over the judicially created doctrine of obvious-type double patenting as being unpatentable over various claims in U.S. Patent Nos. 5,981,505, 5,817,637, 5,830,876 and 5,593,972. At this time, no claims have been allowed in the instant application. Applicants shall file terminal disclaimers as appropriate upon identification of allowable subject matter. Applicants invite the Examiner to telephone Applicants' undersigned representative at 215-665-6928 to arrange to have such terminal disclaimers transmitted to the USPTO by facsimile upon such identification of allowable subject matter.

Conclusion

The claims are in allowable form. An indication that the claims are in condition for allowance is earnestly solicited.

Respectfully submitted,

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Attachments:
1. Abstract of *Mongr Allegery* (1988) 23:225-35.
2. Abstract of *J. Pediatrics* (1999) 134:589-96.
3. Abstract of Turk J. Pediatr. (1992) 34:203-9.
4. Package Insert for BayTet® (Tetanus Immune Globulin (Human))
5. Package Insert for BayRab® (Rabies Immune Globulin (Human))
6. Package Insert for BayGam® (Immune Globulin (Human))
7. Package Insert for BayHep B® (Hepatitis B Immune Globulin (Human))